REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1 and 8 are currently being amended.

New claim 60 is added. Support for this claim is found in Example 13 as compound 000202.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1, 8, 13, 22-24 and 57-60 are now pending in this application.

Summary of Examiner Interview

Applicant thanks the Examiner for the courtesy extended to Applicant's counsel, Tom Moran (Reg. No. 26,314) and Wenrong Huang (Reg. No. 58,012), during the telephone interview on August 28, 2007 regarding the present Final Office Action. In accordance with the procedure outlined in M.P.E.P. § 713.04, the following is a summary of the interview.

1. No exhibits were shown nor was any demonstration conducted.

2. Claims 1 and 13 were discussed.

3. The prior art discussed was Potier, et al (FR 2837824) and Pan et al (Yaoxue Xuebao 1997, 32(12), 898-901).

4. Applicant's counsel discussed the proposed amendment to claim 1 to delete

pyridine-3-yl as R_1.

5. During the interview, Applicant's counsel informed the Office of Applicant's intention to amend claim 1 to delete pyridine-3-yl as R_1 and therefore overcome the rejection under 35 U.S.C. § 102(b) over Potier et al. Further, Applicant's attorney presented the arguments that Potier et al does not render claim 1 as amended obvious because Potier et al does not teach a generic heteroaryl group as R_1 nor does it teach the specific thymin-1-yl as R_1. Applicant's attorney also presented the arguments that Pan et al does not render claim 13 obvious because Pan et al does not teach furanyl group substituted on the furan ring with any substituent, particularly not 5-nitro.

6. No other pertinent matters were discussed.

7. Applicant's attorney offered claim amendments but the Examiner did not opine on the acceptability of these proffered claim amendments to remove the outstanding rejections. However, the Examiner has agreed to consider Applicant's amendment and arguments once they are filed with the Office. The Examiner has also suggested Applicant submit any additional data that are available to support the patentability of the claims.

Claim Rejections

35 U.S.C. § 112

Claims 1, 8, 13, 22-24 and 57-59 stand rejected under 35 U.S.C. § 112. while acknowledging that one compound claimed in claim 1, podophylotoxin-4-O-ester of thymin-1-acetic acid, is enabled by the application, see Office Action at page 2, the Office Action alleges that "the specification fails to provide sufficient support of the broad claims of the compound for treatment of various types of cancer" and that "one of ordinary skill in the art would have to engage in undue experimentation to test which disease can be treated" by the claimed compounds, see Office Action at page 6.

To support this conclusion, the Office Action cites the factors listed by the Federal Circuit in *In re Wands*, 858 F..2d 731, 737, 8 USPQ.2d 1400, 1404 (Fed. Cir. 1958). The Office Action states that the invention is related to podophyllotoxin derivatives that are useful for treating various types of cancer. The Office Action further states that the state of art is screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities and that there is no absolute predictability and that each embodiment is required to be individually assessed for physiological activity due to the high level of unpredictability. The Office Action then states at length how *in vitro* data cannot duplicate the complex conditions of the *in vivo* environment because cells in culture exhibit different characteristics. Next, the Office Action states that the specification only provides toxicity or efficacy information for one compound and that not all similar compounds have been shown to have effect at a given concentration as shown in the Table on page 51. Finally the Office Action characterizes the breath of the claims as treating various types of cancer and that a person skilled in the art would need to determine the particular link and substitution on the R_1 group that would provide a compound with desired activity. The Office Action then concludes that such determination will constitute undue experimentation under the enablement test.

Without acquiescing to the position taken by the Office, Applicant has amended claim 1 to adjust the scope of the claims in order to expedite prosecution. As amended, claim 1 now covers compounds wherein m is 0-3 and R_1 is thymin-1-yl. Similarly, claim 13 as previously presented covers compounds wherein m is 0-3 and R_1 is 5-nitrofuranyl-2-yl. Inasmuch as the rejection is applied to the amended claims, Applicant respectfully traverses this rejection.

In order to make an enablement rejection, the Patent Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, (Fed. Cir. 1993). "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439

F.2d 220, 224 (CCPA 1971). Applicant respectfully submits that the Office has not met its burden in establishing the instant rejection.

First, the Office Action's statements that the specification fails to provide sufficient support of the broad claims of the compound for treatment of various types of cancer and that one is required to engage in undue experimentation to test which disease to treat are not applicable to any of the pending claims. Claims 1, 8, 13 and the now new claim 60 are directed to the claimed compounds only. Claims 22 and 23 are directed to a pharmaceutical composition comprising a compound claimed in claim 1, and claims 57 and 58 are directed to a pharmaceutical composition comprising a compound claimed in claim 13. Claims 24 and 59 are directed to a method of treating breast cancer using a compound of claim 1 or 13, respectively. None of the claims recites treating various types of cancer, and therefore one does not need to test which disease to treat using the claimed compounds.

Second, Applicant submits that the Office has misstated the standard and has overlooked the extend of the disclosure provided by the specification. "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737 (citing *In re Jackson*, 217 USPQ 804, 807 (Bd. App. 1982)).

In particular, in assessing whether a claimed pharmaceutical use is enabled, neither absolute predictability nor assessment of each embodiment is required. The MPEP states that courts have repeatedly held all that is required is a reasonable correlation between the activity and the asserted use. MPEP § 2107.03. "Courts have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility as being supportive of an assertion of therapeutic utility for a new compound." MPEP § 2107.03 (citing *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980)). Further, *in vivo* activity is not required to establish that a claimed compound is useful to treat a certain disease. Data from *in*

vitro testing is generally sufficient to support therapeutic utility if a reasonable correlation exists between *in vitro* assays and the particular therapeutic utility. MPEP § 2107.03.

In the instant case, Applicant submits that the claims are enabled by the specification. The specification has provided both general synthetic process (Specification at pages 18-22) and specific examples (Examples 13 and 16) of making the claimed compounds. The specification also provides detailed description of the pharmaceutical composition of claims 22, 23, 57 and 58. Pages 11 to 14 provides the amount of the compounds that can be included in a claimed pharmaceutical composition, the different types pharmaceutically acceptable excipients that may be combined with the compounds, and different forms of the claimed pharmaceutical compositions. Page 11 of the specification also stated that liposomes, which was recited in claim 58, have been successfully used to administer a cancer medication to a patient. Further, the specification has provided biological assays and results that would enable a person skilled in the art to practice the method of treating breast cancer using the claimed compounds. Example 27 provides directions for an *in vitro* assay for testing compounds of the invention for their effect on cell growth and provides the results for two of the compounds covered by the claims. i.e. the ester of 5-nitro-2-furoic acid (compound 000202, claimed in claims 13 and 60) and the ester of thymine-1-acetic acid (compound 0003061, claimed in claims 1 and 8). Both compounds are shown to be active in inhibiting cell growth under the assay conditions. Example 28 provides directions for performing *in vivo* toxicity tests of the compounds in mice, and Example 29 provides directions for performing *in vivo* efficacy tests of the claimed compounds. The *in vivo* results for compound 0003061 is also provided. In particular, the efficacy data show that the survival rate for tumor-bearing mice treated with compound 0003061 is more than twice of control mice.

The claim of anticancer property of the claimed compounds does not only rely on *in vitro* data. The *in vitro* data show that the claimed compounds are effective in inhibiting cell growth, and the *in vivo* data show that the compounds having inhibitory activity against cell growth are efficacious in increasing survival rate of mice bearing tumors. Therefore, the specification has

shown a good correlation between the *in vitro* data and the *in vivo* activity of the compounds in treating cancer.

As to the number of working examples, Applicant submits that the specification has provided a representative number of examples to enable the entire scope of the claims. Each of claims 1 and 13 covers only compounds wherein m is 0-3 and R_1 is thymine-1-yl and 5-nitro-furan-2-yl, respectively. Claim 8 as amended is specifically directed to compound 0003061 where m is 1 and R_1 is thymine-1-yl. The new claim 60 is specifically directed to compound 000202 where m is 0 and R_1 is 5-nitro-furan-2-yl. The specification provides detailed experimental protocols for testing the claimed compounds *in vitro* and *in vivo*. *In vitro* data are given for an example of each of the thymine-1-yl and 5-nitro-furan-2-yl analogues. Both of the compounds show good activity in inhibiting colony formation, with complete inhibition at a concentration of 100 nM. *In vivo* toxicity and efficacy data are given for the thymine-1-yl compound. The data show a good correlation of *in vitro* activity with *in vivo* efficacy. A person skilled in the art will be able to readily extrapolate the data from the two exemplary compounds to the remaining compounds in the claim scope and use the guidance provided in the disclosed protocol to conduct further testing. Applicant submits that such testing will be routine and not be undue experimentation.

Further, the claims are not directed to treating various types of cancer as alleged in the Office Action. Claims 24 and 59 are directed to treating breast cancer with the claimed compounds. Example 29 and the data on page 51 provide animal experiment procedure and testing results for treating mice with MTG-B tumors, i.e. mammary adenocarcinoma. Therefore the claimed method is fully supported by the specification.

In summary, the specification has provided detailed guidance and experimental data to enable those skilled in the art to make and use the claimed invention, which is narrow in scope. Therefore, withdrawal of the rejection is respectfully requested.

35 U.S.C. § 103

Claims 1, 8, and 22-24 stand rejected under 35 U.S.C. § 103 as being obvious over Potier et al (FR 2837824). The Office Action states that the difference between the prior art and the claims in the instant application is that prior art generically discloses a heteroaryl group and the claims of the instant application claims heterocyclic pyridine compounds that are positional isomers of the compounds disclosed in Potier et al. Without acquiescing to the position of the Office, Applicant has amended claim 1 to delete "optional substituted pyridin-3-yl" as R_1, therefore the rejection is overcome. However, inasmuch as the rejection is applied to the amended claims, Applicant respectfully traverses this rejection.

The test for prima facie obviousness as articulated by the Court of Appeals for the Federal Circuit in *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991) requires consideration of at least the following factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should practice the claimed invention; and (2) whether the prior art would also have provided a reasonable expectation of success to such a skilled artisan. Further, all claim limitations must be taught or suggested by the prior art. MPEP § 2143.03 (citing *In re Royka*, 490 F.2d 981 (CCPA 1974)).

Applicant asserts that the Office has failed to establish a prima facie case of obviousness. Contrary to the statement in the Office Action, Potier et al does not teach generic heteroaryl group as R_1. It only teaches a few specific heteroaryl groups, such as pyridinyl, imidazolyl, thiazolyl and indolyl, as R_1, see page 1-5 of the specification of Potier et al. There is no teaching that R_1 can be any heteroaryl group or any other heteroaryl groups not disclosed by Potier et al. Thus, Potier et al has no teaching or suggestion for using the specific heteroaryl group recited in claim 1, namely thymin-1-yl. Potier et al does not teach all the claim limitations and does not provide a reasonable expectation of success of practicing Applicant's invention. Therefore, claim 1 as amended is not obvious over Potier et al.

Claims 13 and 57-59 stand rejected as being obvious over Pan et al (Yaoxue Xuebao 1997, 32(12), 898-901). The Office Action states that Pan et al relates to podophyllotoxin derivatives with substituted or unsubstituted furanyl carboxylic esters. The Office acknowledges that the furanyl carboxylic acids disclosed therein are not 5-nitro-furanyl carboxylic acid, but alleges that an experienced Ph.D. synthetic organic chemist would be motivated to prepare the nitro substituted analogs.

Applicant respectfully disagrees with Office's characterization of the teaching of Pan et al with regard to substituted furanyl compounds. The two compounds disclosed in Pan et al are 2-furyl and 2-furylethenyl compounds. Neither of them has a substituent on the furanyl ring (the ethenyl is a linker between the furanyl ring and the carbonyloxy group). Therefore, Pan et al does not teach or suggest putting any substituent on the furanyl ring that would motivate a person of ordinary skill in the art to make a substituted furanyl compound, let alone to make the specific 5-nitro-substituted furanyl compound claimed in the instant application. Pan et al does not teach all the claim limitations and does not provide a reasonable expectation of success of practicing Applicant's invention. Therefore, applicant submits that the Office has failed to establish a prima facie case of obviousness.

As such, Applicant respectfully requests that the obviousness rejection be withdrawn.

35 U.S.C. § 102

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Potier, et al. (FR283724). Claim 1 is amended to delete the possibility that R_1 is pyrin-3-yl. As such Applicant respectfully requests that the rejection be withdrawn.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date September 18, 2007

By _____

FOLEY & LARDNER LLP
Customer Number: 38706
Telephone: (650) 251-1185
Facsimile: (650) 856-3710

Wenrong Huang
Attorney for Applicant
Registration No. 58,012